REMARKS

Claims 13, 14-22, 28, and 30-35 are pending in this application. Applicants have cancelled claims 23-27, and 29, and have added new claims 32-35. Claims 13, 15-22, 30, and 31 have been amended. The amendments to claims 13 and 14 are supported by the specification at, for example, page 3, lines 5-17. Support for the amendment to claim 15 can be found in the specification at, for example, page 8, lines 18-20; claims 16, 17, 19, 21, and 28 have been amended for clarity; support for the amendment to claim 18 can be found in the specification at, for example, page 7, lines 25-30; support for the amendment to claim 20 can be found in claim 17, from which it depends. Support for the amendment to claim 22 can be found in cancelled claim 23. Support for the amendment to claim 30 can be found in the specification at, for example, page 5, lines 16-18.

New claims 32 and 33 are supported in the specification at, for example, page 5, lines 16-18. New claims 34 and 35 are supported by pending claims 15 and 20, respectively, prior to their amendment in this reply. No new matter has been added.

The Invention

The invention relates to retroviral vectors that include a viral core of a murine leukemia virus (MLV) and a viral envelope that includes a full-length surface envelope protein and a truncated transmembrane envelope protein from human immunodeficiency virus (HIV) or simian immunodeficiency virus (SIV). These retroviral vectors can be used, for example, to transfer genes into selected cell types, such as CD4-positive mammalian cells. The invention also encompasses methods of preparing packaging cells and methods of using the new retroviral vectors.

Specification

The Examiner noted that there are sequence disclosures in the specification, and that applicants have failed to comply with the requirements of 37 CFR 1.821 through 1.825. Applicants are filing herewith a response to the Notice to Comply With Requirements For Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures

received in this application. Accordingly, applicants respectfully request that this objection be withdrawn.

Claim Objections

The Examiner objected to several informalities present in claims 13, 17, 21, 23, 25, and 26. The informalities concerned, primarily, grammatical errors. Applicants have amended claims 13, 17, and 21 to incorporate the Examiner's suggestions. Applicants have cancelled claims 23, 25, and 26. Accordingly, the stated objections should now be withdrawn.

35 U.S.C. § 112, ¶ 2

Claims 13-31 were rejected for allegedly being indefinite. More specifically, claim 13 was rejected because the Examiner found it was "not clear whether [the] full-length surface envelope protein is from HIV or SIV or whether it can come from any non-HIV/SIV virus comprising a viral envelope" (Office Action at page 4). Applicants have amended claim 13 to clarify the origin of the envelope protein.

Claim 14 was also rejected as being indefinite because of the phrase "wherein the transmembrane envelope protein ... is a truncated variant." The Examiner states that it is "unclear how 'truncated variant' is defined in this context or [how] the limitation distinguishes itself from a 'truncated transmembrane envelope protein' (or further limits it)" (Office Action at page 4). Claim 14 has been amended so that it no longer recites "a truncated variant."

Claim 15 is rejected as indefinite because it is "unclear what is meant by 'are each independently'" (Office Action at page 4). Applicants have amended claim 15 by deleting the term "are each independently" and by otherwise clarifying the subject matter claimed.

Claim 16 is rejected as indefinite for several reasons. First, the Examiner finds that the limitation "any other fragment of the transmembrane envelope protein of a murine leukemia virus" lacks antecedent basis (Office Action at page 5). Claim 16 has been amended so that it no longer contains this language. Therefore, an antecedent basis is not required. Second, the Examiner finds that "it is not clear as to what 'C-terminus' is directed or what is meant by 'modified' in the context of fusion to the 'C-terminus' or 'to any other fragment'" (Office Action at page 5). In response, applicants have amended claim 16 for clarity. Claim 16 now recites that

the C-terminus of a truncated transmembrane protein of HIV or SIV is fused to a fragment of an MLV transmembrane envelope protein.

Claim 17 is also rejected as indefinite for several reasons. First, the Examiner finds insufficient antecedent basis for the limitation "the transfected packaging cell" (Office Action at page 5). In response, claim 17 has been rephrased so that no antecedent basis for "the transfected packaging cell" is required.

Second, the Examiner finds that claim 17 recites the term "psi-negative expression construct", which allegedly "is not defined in the specification" (Office Action at page 5). To the contrary, the specification contains a clear definition of a psi-negative expression construct. See page 1, lines 18-26, where applicants state (emphasis added):

> On the one hand, a packaging cell is required, that provides the *gag-*, *pol-* and *env*-gene products of MLV upon expression of psi-negative constructs so that these genes cannot be packaged into a retrovirus. "psi" designates the packaging signal of retroviruses, that mediates efficient packaging of messenger RNA ...The genes *gag-*, *pol* and *env* within the untreated packaging cell must be psi-negative to prevent the respective messenger RNA from being packaged into retroviral particles."

This passage clearly teaches that a "psi-negative expression construct" is an expression construct that lacks the packaging signal "psi," and this would be understood by one of ordinary skill in the art.

Third, the Examiner contrasts the claim limitation "psi-negative expression construct" with the specification's teaching that "the expression construct has to contain the packaging signal 'psi' (*sic.*)" (Office Action at page 5, citing the specification at page 1, line 24). Applicants traverse this rejection. The method for preparing a packaging cell, as now claimed in claim 17, requires one to transfect a cell with both a psi-negative *and* a psi-positive expression construct. Thus, the requirement of the specification as filed -- that the packaging signal psi has to be present -- is fulfilled. There is no discrepancy between the teaching of the specification and the limitations of claim 17.

Fourth, claim 17 is rejected as indefinite "because the method steps do not relate back to" the preamble, but rather appear to refer to a method for producing retroviral vectors (Office Action at pages 5 and 6). Applicants traverse this rejection. The preamble is not just "a method

for preparing a packaging cell." The preamble, in its entirety, is "a method for preparing a packaging cell that produces a retroviral vector." As claim 17 now reads, the method steps generate a packaging cell that produces a retroviral vector. Accordingly, there is an appropriate relationship between the preamble and the conclusion of the claim.

Fifth and finally, claim 17 is rejected as indefinite because it is allegedly unclear how the phrase "to be transferred ... is related to methods for preparing packaging cells, how the term 'transferred" is defined in context, or what it is directed to" (Office Action at page 6). The term "to be transferred" has been deleted from claim 17. Accordingly, the ground for rejection is now moot.[1]

Similarly, claim 18 was rejected because the method steps allegedly failed to relate back to the preamble and on the basis of the term "to be transferred" (Office Action at pages 5-6). Claim 18 has been amended so that there is an appropriate relationship between the preamble and the conclusion of the claim, and the term "desired gene product to be transferred" has been replaced with the term "a therapeutic gene, a reporter gene, or a biologically active fragment of a therapeutic or reporter gene."

Claim 20 is rejected as indefinite because it is allegedly unclear how "the expression construct" recited in claim 20 relates to the "expression construct" of claim 17 (Office Action at page 6). To avoid ambiguity, applicants have amended claim 20 so that it no longer recites "the expression construct," but rather specifies that the envelope protein is encoded by a vector comprising pLβAc/env-Tr712-neo *et seq.*

Claim 22 is rejected as indefinite because it includes the phrase "further comprising a therapeutic or reporter gene or fragment thereof' (Office Action at page 6). The Examiner argues that "it is unclear how 'therapeutic' and 'fragment thereof' are defined, what their metes and bounds are, or what 'fragment thereof' is directed to" (Office Action at page 6). The Examiner's attention is directed to the amendment of claim 22, which clarifies the components

[1] The Examiner concludes the discussion of claim 17 by stating, "[f]urther, since it is not clear what defines the metes and bounds of 'packaging cells' as set forth in claim 17, it is not possible [to] evaluate the metes and bounds of 'packaging cells' as set forth in claim 21" (Office Action at page 6). Applicants believe the present amendment of claim 17, which addresses each of the Examiner's concerns (see above), also clarifies the metes and bounds of packaging cells. Thus, there is now no impediment to evaluating the metes and bounds of claim 21.

within the composition and their relationship. One of ordinary skill in the art would understand the definition of "therapeutic" and all of the remaining terms in this claim.

Claims 24 and 30 are rejected as indefinite because it is allegedly unclear how the step "inserting into the retroviral vector an mRNA" is performed (Office Action at paragraph bridging pages 6 and 7). Applicants have cancelled claim 24, thus rendering its rejection moot. Applicants do not see how this ground for rejection could apply to claim 30, because that claim does not recite the phrase in question. Claim 30 does require a step of inserting a sequence into a retroviral vector, and one of ordinary skill in the art would have no difficulty in performing this step. Applicants' claim need not specify exactly how the sequence is inserted to be definite.

Claims 24 and 30 are also rejected as indefinite because the double recitation of "the retroviral vector" is allegedly ambiguous (Office Action at paragraph bridging pages 6 and 7). As stated above, applicants have cancelled claim 24, thus rendering it rejection moot. Applicants have amended claim 30 to clarify the distinction between the first and second uses of "the retroviral vector" by modifying the second with phrase "containing the inserted HIV-inhibiting gene or the fragment thereof."

Claims 29 and 31 are both rejected as indefinite because the meaning of the recited phrase "active agent" is allegedly unclear (Office Action at page 7). Applicants have cancelled claim 29, rendering its rejection moot. To clarify the meaning of claim 31, applicants have amended that claim by replacing "active agent" with "biologically active polypeptide," a term that is well known to one of ordinary skill in the art.

Claim 30 is rejected for several reasons. Claim 30 is rejected as indefinite because the phrase "HIV-inhibiting gene or a fragment thereof" is allegedly unclear (Office Action at page 7). Applicants have amended claim 30 so that it no longer includes this phrase. Instead, one inserts a particular sequence (*e.g.*, one encoding an antisense sequence that inhibits HIV) into the retroviral vector. The metes and bounds of amended claim 30 are clear. The Examiner also objected to the term "the foreign gene" as lacking antecedent basis (Office Action at page 7). The term "the foreign gene" is no longer included in claim 30. Further, claim 30 is rejected because the claim does not provide for transfer of the "fragment thereof" in the final transfection step" (Office Action at page 7). Claim 30 no longer recites the phrase "fragment

thereof." Therefore, it would be inappropriate to refer to that phrase in the final transfection step.

Claim 31 is also rejected as indefinite because it does not provide for transfer of "a fragment thereof" in the final transfection step (Office Action at page 7). Applicants have addressed this concern by adding the phrase "or the fragment thereof" to the final clause of the claim. Further, claim 31 is rejected because it is allegedly "unclear whether 'active agent' is directed to 'fragment thereof' only or to both 'fragment thereof *and* the 'foreign gene'" (Office Action at page 7). The amendment to claim 31 removes any alleged ambiguity, as it is clear that "agent" (now amended to "biologically active polypeptide") refers to both "gene" and "fragment thereof."

In view of the foregoing, applicants respectfully request that the rejection for lack of clarity be withdrawn. *Should the Examiner decide to maintain any of these grounds for rejection (or impose new grounds for rejection), the favor of a telephone call to the undersigned is requested.*

35 U.S.C. § 112, ¶ 1

Claims 13, 15, and 22-31 are rejected under the first paragraph of 35 U.S.C. §112 for lack of an adequate written description (Office Action at pages 8-9). More specifically, the Examiner states (Office Action at page 8; emphasis added):

> [c]laims 13, 15, and 22-31 recite compositions and methods comprising a retroviral vector comprising a full-length surface envelope protein from any retrovirus other than HIV or SIV.

In response, the Examiner's attention is directed to amended claim 13 (from which claims 15, 22, 28, 30, and 31 depend). As amended, claim 13 covers a retroviral vector comprising a viral core of MLV and a virus envelope comprising a full-length surface envelope protein of HIV or SIV and a truncated transmembrane envelope protein of, again, HIV or SIV. While applicants' specification provides an adequate written description for broader or different claims, those now pending do not require inclusion of full-length surface envelope proteins from retroviruses *other than* HIV or SIV. Accordingly, there is no basis for the rejection on this ground.

The Examiner also states that there is no evidence that "Applicants contemplated or were in possession of retroviral vector[s] comprising *full-length* ... transmembrane envelope proteins of HIV or SIV" (Office Action at page 8). The term "full-length ... transmembrane envelope protein" has been deleted from claim 13. Accordingly, there is no basis for the rejection on this ground.

With respect to claims 22 and 24, the Examiner states, "there is no evidence of record indicating that Applicants contemplated or were in possession of retroviral vectors capable of mediating transfer of genetic and/or therapeutic material into any cells other than CD4-positive mammalian cells" (Office Action at page 9). Claim 22 has been amended to state, "the vector mediates the transfer of the therapeutic gene ... *into a CD4-positive cell of a mammal*" (emphasis added). Accordingly, there is no longer a basis for this rejection.

Claims 13 and 24-29 are also rejected as allegedly lacking enablement, "because the specification, while being enabling for pseudotypic retroviral vectors comprising MLV cores, full-length HIV or SIV surface envelope proteins and truncated HIV or SIV transmembrane envelope proteins mediated transfer into CD4-positive mammalian cells, does not reasonably provide enablement for retroviral vectors comprising full-length transmembrane envelopes from HIV or SIV mediating transfer into any other 'specific cell type'" (Office Action at page 9). As noted above, claim 13 has been amended and, as amended, covers subject matter the Examiner has found enabled. Claims 24-27 and claim 29 have been cancelled; claim 28, which depends from claim 13, is already restricted to transfer into a CD4-positive cell. Accordingly, claims 13 and 28 are enabled.

Claims 19, 20, 22, 23, and 29-31 are rejected as lacking enablement because they relate to subject matter allegedly not "readily available to the public or...obtainable by a reproducible method set forth in the specification" (Office Action at page 11). In particular, the Examiner indicated that the cell line TelCeB6 and the expression plasmids pLßAc/env-Tr712-neo and pMB2 are not readily available to the public or obtainable by a reproducible method set forth in the specification (Office Action at page 11). The Examiner further indicated, "one of skill in the art would readily recognize that no two stably-transformed cell lines are identical or reproducible" (Office Action at page 11).

Applicants first note that the arguments above are relevant only to claims 19 and 20. Second, applicants note that the cell line TelCeB6 can be obtained from Cosset *et al.* Even if the Examiner considers that source somewhat unreliable, cell lines are made routinely by those of ordinary skill in the art, and nothing on the record indicates that the cell line used must have all the characteristics of the TelCeB6 cell line (nor does the Examiner explain *why* making a cell line would require undue experimentation). What is required is a cell line comprising a *gag* gene of MLV, a *pol* gene of MLV, and an expression construct. Cells of such a cell line can be made with routine methods. Plasmids are even easier to construct, and identical plasmid preparations are made frequently by those of ordinary skill in the art.

Claims 22, 23, 29, 30, and 31 are rejected as lacking enablement because "these claims are drawn to methods of gene therapy that are not enabled by the instant disclosure" (Office Action at page 11). The Examiner states that "since gene therapy was not routinely performed at the time the invention was made, it is imperative that Applicants *specification* – not the prior art – provide a basis for establishing that they have overcome the problems in the art and further provide specific guidance on how to use the vectors of the instant invention to treat disease" (Office Action at page 12), and later states that "the various statements invoking the results of Lodge bear no probative value in overcoming the prima facie case against enablement –what matters is the guidance provided in the instant specification (Office Action at page 12).

Applicants traverse this ground for rejection because it contradicts the legal standard for judging whether a claim is enabled. As the MPEP states at 2164.01 (citing *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988):

> The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent **coupled with information known in the art** without undue experimentation ... A patent need not teach, and preferably omits, what is well known in the art. (Emphasis added.)

The proper legal standard for enablement mandates scrutiny of both the specification **and the prior art**. Moreover, considerable experimentation is allowed, so long as it is in keeping with the level of experimentation routinely practiced in the art. Gene therapy *per se* need not be routine for applicants' specification to enable the present claims.

Applicants also challenge the Examiner's interpretation of the words "possibilities" and "develop" to mean that the specification discloses only "the possibility of developing a strategy for gene therapy" (Office Action at paragraph bridging pages 13 and 14). In the context of the specification as a whole these words illustrate that the invention makes possible, among other things, the transduction of a cell with a gene via a retroviral vector. The specification provides more than a mere hope of transducing a cell with a gene via a retroviral vector.

Given applicants' amendments, the arguments here, and those previously of record, it would not require undue experimentation for one of ordinary skill in the art to practice the invention as claimed. The invention as claimed is enabled, and this ground for rejection can be withdrawn.

35 U.S.C. § 102(a)

Claims 15 and 20 are rejected under 35 U.S.C. §102(a) as anticipated by Schnierle *et al.* (*Proc. Natl. Acad. Sci. USA*, 94:8640-8645, 1997). Although applicants claim the benefit of the earlier filing date of German application No. 197707971.7, and have provided a certified translation of that application, the Examiner argues that (Office Action at page 15):

> Claims 15 and 20 recite subject matter not disclosed in German application No. 197707971.7. Since the German application fails to disclose *all* of the specific envelope protein or expression construct embodiments the rejection would still apply to newly amended claims 15 and 20.

Claim 15 specifies that the retroviral vector of claim 13 is one in which the full-length surface envelope protein is an HIV type 1 or an HIV type 2 surface envelope protein or an SIV envelope protein. This vector is disclosed in the German application at, for example, page 2, line 31, to page 3, line 8. Claim 20 has been amended to cover a retroviral vector in which the envelope protein is encoded by the plasmic pLβAc/env-Tr712-neo. This vector is disclosed in the German application, for example, in claim 8.

Accordingly, the German application *does* disclose the specific envelope protein or expression construct embodiments now claimed. This ground for rejection should be withdrawn.

35 U.S.C. § 102(f)

The Examiner has maintained the rejection of claims 13-29 on the ground that the present applicants did not invent the claimed subject matter (Office Action at page 15). Applicants understand the Examiner's point with respect to their argument that since Dr. Schnierle was not named as co-author on two additional journal articles from the same laboratory published after 1997, she did not contribute to the presently claimed invention. Applicants fail to understand, however, why the Examiner has disregarded their contention that Dr. Schnierle contributed only to specific parts of the 1997 paper, but not to the subject matter that is presently claimed. Applicants respectfully request further guidance on the showing they must make to overcome this ground for rejection.

35 U.S.C. § 103

Claims 13-29 are rejected under 35 U.S.C. §103(a) as obvious over Denesvre *et al.* (J. Virol., 70:4380-4386, 1996) in view of Salmons *et al.* (Leukemia, 9(Suppl.):S53-S60, 1995) and either Wilk *et al.* (Virology, 189:167-177, 1992) or Zingler *et al.* (J. Virol. 67:2824-2831, 1993) (Office Action at paragraph bridging pages 16 and 17). Applicants traverse this rejection.

To establish such a *prima facie* case, the Examiner must make three showings. First, the Examiner must show that there is "some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings". MPEP §2142. Second, the Examiner must demonstrate that there is "a reasonable expectation of success." MPEP §2142. Third, the Examiner must demonstrate that the prior art reference (or references, when combined) "teach or suggest all the claim limitations." MPEP §2142. Applicants respectfully submit that the Examiner has still not established a *prima facie* case of obviousness.

Applicants reassert the arguments of record (see the paper filed September 11, 2000). Moving beyond the arguments of record, applicants note that the courts have strictly applied the requirement for "motivation" to combine reference teachings. For example, the Court of Appeals for the Federal Circuit recently characterized the requirement as "an essential evidentiary component" that must be "clear and particular" not "conclusory." Brown &

Williamson Tobacco Corp. v. Philip Morris Inc., 229 F.3d 1120, 1124-25, 56 USPQ2d 1456, 1459 (Fed. Cir. 2000). More specifically, the court said (emphasis added):

> The first requirement is that a showing of a suggestion, teaching, or motivation to combine the prior art references is an 'essential evidentiary component of an obviousness holding.' C.R. Bard, Inc. v. M3 Sys. Inc., 157 F.3d 1340, 1352, 48 USPQ2d 1225, 1232 (Fed. Cir. 1998)...This showing must be clear and particular, and broad conclusory statements about the teaching of multiple references, standing alone, are not 'evidence.'

Applicants fail to see, in any of the Examiner's statements, any "clear and particular" showings of suggestion or motivation to combine references. Instead, the Examiner has impermissibly relied on "conclusory" statements. For example, the Examiner states that the "rule" of Denesvre *et al.* "implicitly provides a solution to the problem of making MLV/HIV-1 pseudotypes *as suggested by Salmons, who clearly provided the motivation to do so*" (Office Action at page 17; emphasis added). Here the Examiner does not provide "clear and particular" support for the suggestion or motivation allegedly offered by Salmons *et al.*, but rather, merely offers impermissible "broad conclusory statements" about the suggestion and motivation. Later, the Examiner argues that a lack of suggestion in Zingler *et al.* (that is, "use of truncated SIV envelope proteins to pseudotype MLV-viral cores") "is not a deficiency given...Salmon's motivation..." (Office Action at page 18). However, the Examiner again fails to offer the requisite support, instead offering an impermissible conclusory statement. On this basis alone, the rejection for obviousness should be withdrawn.

Furthermore, even if Denesvre *et al.* in view of Salmons *et al.* and either Wilk *et al.* or Zingler *et al.* were somehow alleged to provide a motivation to make the presently claimed invention, the Office Action still fails to show the requisite reasonable expectation of success to support a *prima facie* case. Thus, the rejection should be withdrawn.

In addition, the Examiner points out that Denesvre *et al.* describes the "simple rule that retroviral cores allow incorporation of heterologous envelopes whose cytoplasmic tails are smaller than that of the original parental envelope" (Office Action at page 17), and then, reasons that "since HIV and SIV are retroviruses, this rule would clearly apply to the claimed subject-matter of the instant invention" (Office Action at page 17). The Examiner concludes that Denesvre *et al.* "implicitly provides a solution to the problem of making MLV/HIV-1

pseudotypes as suggested by Salmons *et al.*, who clearly provided the motivation to do so" (Office Action at page 17).

Applicants question this view of the prior art because before the priority date of the present application there were no reports regarding the generation of HIV/SIV-Env-pseudotyped MLV-based vectors. It is true that Denesvre *et al.* describe several experiments investigating the influence of complete, truncated, or chimeric Friend murine leukemia virus (F-MuLV) and human T-cell leukemia virus type 1 (HTLV-1) transmembrane (TM) protein domains on incorporation into virions and on infectivity. As already cited by the Examiner, Denesvre *et al.* further discloses that "HIV-1 Env containing a long cytoplasmic tail is not incorporated into MuLV particles" (Denesvre *et al.*, p.4385, left col., 3rd para) and suggests the above-cited "simple rule."

However, contrary to the Examiner's assertions, a person of ordinary skill in the art would not necessarily have concluded that the simple rule suggested in Denesvre *et al.* also applied to retroviral vectors comprising the MLV core and HIV/SIV envelope of the invention as claimed. In fact, Denesvre *et al.* is exclusively directed to MLV-particles containing "complete, truncated, or chimeric Friend murine leukemia virus (F-MuLV) and human T-cell leukemia virus type 1 (HTLV-1) envelopes" (Denesvre *et al.*, page 4380, abstract), and does not refer to a retroviral vector comprising a MLV core and a virus envelope comprising a HIV/SIV envelope as claimed in the present application. There is no suggestion in Denesvre *et al.* of such pseudotypes.

Denesvre *et al.* further demonstrate that certain chimeric envelopes "which are readily fusogenic in cell-to cell assays and also efficiently incorporated into virions may not necessarily confer virus-to-cell fusogenicity" (Denesvre *et al.*, page 4380, abstract), which led the authors to conclude that "requirements for cell-to-cell fusion and virus-to-cell fusion mediated by retroviral envelopes are distinct" (Denesvre *et al.*, page 4385, left column, 1st paragraph). This conclusion demonstrates that the "simple rule" of Denesvre *et al.* is actually speculative in nature. Accordingly, Denesvre *et al.* cannot be considered to provide a solution to the problem of generating the pseudotyped retroviral vectors as claimed in the present application.

Furthermore, Salmons *et al.* does not provide the motivation to generate MLV/HIV-1 pseudotypes, despite the Office's conclusory statement that it does (Office Action at page 17).

As applicants indicated in the response to the previous Office Action, Salmons *et al.* states that "it appears that a mere co-production of HIV Env in an MLV Gag and Pol producing packaging cell line may not be sufficient to ensure efficient production of MLV-HIV-pseudotypes (Salmons *et al.*, page S58, left col., 2nd paragraph of section "Discussion"). Accordingly, Salmons *et al.* merely demonstrates that further experimentation will be necessary in order to obtain infectious MLV/HIV-1 pseudotypes. Without providing any guidance on the further experimentation necessary, Salmons *et al* cannot render the claims 13-29 obvious.

Thus, Denesvre *et al.* and Salmons *et al.*, either alone or combination, fail to suggest the subject matter of claims 13-29. Nor can Wilk *et al.* or Zingler *et al.* cure the deficiencies of Denesvre *et al.* and Salmons *et al.* The Examiner has failed to make the requisite showing that any of these references, either alone or in combination, render the claimed invention obvious.

In light of the above, applicants respectfully request that these grounds for rejection be withdrawn.

CONCLUSION

In view of the foregoing, the present claims are in condition for allowance, which action is respectfully requested.

Attached is a marked-up version of the changes being made by the current amendment.

Enclosed is a $2700 check for the fee for the RCE and for the required Extension of Time. Applicants also enclose a Petition for a Five-Month Extension of Time. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 11649-002001.

Respectfully submitted,

Date: December 11, 2001

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Version with Markings to Show Changes Made

In the specification:

Please replace the existing sequence listing with the paper copy of the new sequence listing filed herewith.

In the claims:

Claims 23-27 and 29 have been cancelled.

Claims 32-35 have been newly added.

Claims 13, 14-22, 28, 30 and 31 have been amended as follows:

13. (Amended) A retroviral vector comprising

a viral core of murine leukemia virus (MLV); and

a virus envelope[,] comprising a full-length surface envelope protein of human immunodeficiency virus (HIV) or simian immunodeficiency virus (SIV), and a [full-length or] truncated transmembrane envelope protein of [human immunodeficiency virus (HIV) or simian immunodeficiency virus (SIV)] HIV or SIV.

14. (Amended) The retroviral vector of claim 13, wherein the truncated transmembrane envelope protein [of] is an HIV [or SIV is a truncated variant] truncated transmembrane envelope protein.

15. (Amended) The retroviral vector of claim 13, wherein (a) the full-length surface envelope protein [are each, independently, a human immunodeficiency virus (HIV) type 1, (HIV) type 2, simian immunodeficiency virus (SIV) of *Cerecopithecus aethiops* (SIVagm), SIV of *Macaca mulatta* (SIVmac), SIV of *Pan troglodydytes* (SIVcpz), SIV of *Cerecopithecus mitis* (SIVsyk), SIV of *Papio sphinx* (SIVmnd), SIV of *Cercocebus atys* (SIVsm), or SIV of *Macaca nemestrina* (SIVmne), surface envelope or transmembrane envelope protein] is an HIV type 1 or an HIV type 2 surface envelope protein or an SIV surface envelope protein and (b) the

transmembrane envelope protein is an HIV type 1 or an HIV type 2 transmembrane envelope protein or an SIV transmembrane envelope.

16. (Amended) The retroviral vector of claim [14] 13, wherein the C-terminus of a truncated [variant of the] transmembrane envelope protein of HIV or SIV is [modified by fusion to the C-terminus or of any other fragment of the transmembrane envelope protein of a murine leukemia virus (MLV) or of any other retrovirus] fused to a fragment of an MLV transmembrane envelope protein.

17. (Amended) A method for preparing a packaging [cells] cell that [produce] produces a retroviral vector, the method comprising transfecting [cells] a cell with

(i) a psi-negative expression construct comprising [the *gag*-genes] a *gag* gene and [the *pol*-genes] a *pol* gene of murine leukemia virus (MLV);

(ii) a psi-positive expression construct encoding a desired gene product [to be transferred]; and

(iii) a transcriptional cassette encoding an envelope protein of human immunodeficiency virus (HIV) or simian immunodeficiency virus (SIV)[;], thereby generating a packaging cell [wherein the transfected packaging cell is able to produce] that produces a retroviral vector comprising a viral core of MLV and a virus envelope comprising an envelope protein of HIV or SIV.

18. (Amended) A method for preparing a packaging [cells] cell that [produce] produces a retroviral vector, the method comprising:

obtaining [cells] a cell of a packaging cell line comprising a *gag*-gene and a *pol*-gene of murine leukemia virus (MLV) and an [expression-construct] expression construct encoding a therapeutic gene, a reporter gene, or a biologically active fragment of a therapeutic or reporter gene; [desired gene product to be transferred]; and

transfecting [cells] the cell of the packaging cell line with a construct comprising a transcriptional cassette encoding an envelope protein of human immunodeficiency virus (HIV) or simian immunodeficiency virus (SIV)[;], thereby generating a packaging cell

[wherein the transfected packaging cell is able to produce] that produces a retroviral vector comprising a viral core of MLV and a virus envelope comprising an envelope protein of HIV or SIV.

19. (Amended) The method of claim 18, whereby the cell[s] of the packaging cell line to be transfected is a [are] cells of the packaging cell line TELCeB6.

20. (Amended) The method of claim 17, [whereby the expression construct is an *env* expression construct comprising] wherein the envelope protein is encoded by a vector comprising pLβAc/env-Tr712-neo[, pRep *Δ16 env*, pRep *Δ7 env*, pRep *Δ0 env*, pRep *Δ7MLV env,* or pRep *Δ0MLV env*].

21. (Amended) [Packaging cells] A packaging cell prepared by the method of claim 17.

22. (Amended) A composition comprising a retroviral vector of claim 13, [further comprising] wherein the retroviral vector further comprises a therapeutic gene, a [or] reporter gene, or a biologically active fragment of a therapeutic gene or reporter gene [thereof], wherein [said] the vector mediates the transfer of the therapeutic gene, the [or] reporter gene, or the fragment [thereof] of the therapeutic gene or reporter gene into a [specific cell type] CD4-positive cell of a mammal.

28. (Amended) A composition comprising a retroviral vector of claim 13, [further comprising] wherein the vector further comprises a foreign gene or a fragment thereof[, wherein said vector mediates the transfer of the foreign gene or fragment thereof into a CD4-positive cell to genetically modify the cell].

30. (Amended) A method of treating a human immunodeficiency virus (HIV) infection in an individual; the method comprising

[obtaining] providing a retroviral vector of claim 13;

inserting into the retroviral vector [a foreign HIV-inhibiting gene or a fragment thereof; and] a sequence encoding an antisense molecule, a sequence encoding an RNA decoy, or a sequence comprising a transdominant-negative mutant gene of HIV or of another lentivirus, thereby producing a retroviral vector that inhibits HIV; and

transfecting CD4-positive cells of the individual with the retroviral vector that inhibits HIV [to transfer the foreign gene into the CD4-positive cells], thereby treating the HIV infection.

31. (Amended) A method of treating a genetic disorder in an individual, the method comprising

[obtaining] providing a retroviral vector of claim 13;

inserting into the retroviral vector a [foreign] gene or a fragment thereof encoding an biologically active [agent] polypeptide, thereby producing a therapeutic retroviral vector; and

[transfecting] transducing cells of the individual with the therapeutic retroviral vector to transfer the foreign gene or the fragment thereof into the cells, thereby [to enable] enabling the cells to express the [active agent,] biologically active polypeptide, thereby treating the genetic disorder.